REMARKS

Claims 2-12, 17 and 31-50 were pending in the application. Claims 31-43 and 48-50 have been cancelled as drawn to non-elected invention. New claims 51-56 have been added. Support for the new claims can be found in throughout the specification, for example, at page 11, line 24 to page 12, line 4.

Applicants' note that claims 3-5, 7, and 9 remain withdrawn from consideration pursuant to the election of the species KRRLIFSK ***with traverse*** in Paper No. 10. The species election was for searching purposes only, and it is Applicants' understanding that upon allowance of the elected claims, the claims reading on the remaining species also will be searched and Applicants will be entitled to consideration of claims to the additional species. MPEP 803.02.

Accordingly, upon entry of the Amendment, claims 2-12, 17, 44-47 and 51-56 will be pending. For the Examiner's convenience, a clean copy of all the pending claims is set forth in Appendix I.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Claim Rejections Under 35 USC §103(a)

The rejection of claims 2, 6, 8, 10-12, 17 and 44-47 remain rejected as unpatentable over WO 94/09135 (Beach *et al.*) in view of Xiong *et al.*(1993). Specifically, the Office Action states that:

> Beach discloses that drugs which alter p21 function can be used to inhibit or enhance cell division (page 25, lines 22-23), and that these drugs can be small peptides which mimic the complex constituent in terms of binding but which lacks its active region (page 25, lines 25-26). Therefore, the Beach reference teaches that peptides derived from p21 can be used to inhibit cyclin D1 complex formation, and Beach also discloses methods of identifying such peptides.

Applicants respectfully traverse this rejection for the following reasons.

Beach *et al.* teach that cyclin D1, Cdk4, p21 and PCNA form a quaternary complex. They further teach that this quaternary complex is involved in cell cycle

regulation, generally propose that agents which prevent complex formation by interfering with *any of the constituents* of the complex would be useful in modulating cell division, and describe general screening assays to identify such agents. However, Applicants respectfully point out that such general teachings as those found in Beach *et al.* amount to nothing more than an invitation to embark on a research program to identify molecules capable of disrupting interactions between constituents of the p21/Cdk4/cyclinD1/PCNA complex.

For example, Beach *et al.* merely mentions that agents that inhibit formation of the quaternary complex could be small peptides which mimic binding of one of the constituents but which lack its active region. However, Beach *et al.* fail to provide any guidance whatsoever as to the identity of a single peptide that has these characteristics. Indeed, completely lacking in the teachings of Beach *et al.* are the identities of the active regions or binding sites of any of the four constituents of the quaternary complex, let alone peptides of p21 as used in the presently claimed invention.

Further, Beach *et al.* merely propose general screening assays to identify molecules that disrupt the quaternary complex (see, pages 26-27). There is no mention of whether a direct interaction between p21 and cyclin D, or p21 and Cdk4 even exists in the absence of the other members of the complex. Thus, the presently claimed assays, which are directed to identifying a compound that interferes with p21/CDK4 or p21/cyclin D interaction, were not even contemplated by Beach *et al.*

Even if, *in arguendo*, Beach *et al.* could be interpreted to encompass methods to identify inhibitors of p21, this reference still fails to teach the presently claimed methods which *use peptide fragments of p21* in assays to identify compounds that modulate the interaction of p21 with cyclin D or CDK4. The screening assays suggested by Beach *et al.* to identify agents that disrupt the quaternary complex use the components of the complex, *i.e.*, cyclin D, CDK4, p21 and PCNA. Indeed, there is absolutely no mention by Beach *et al.* that anything but full-length cyclin D, CDK4, p21 and PCNA could or should be used in screening assays to identify useful drugs. This is due at least in part to the fact that, prior to Applicants' invention, the *binding sites of p21 were unknown.*

Xiong *et al.* was cited to "exemplify that the sequence of p21 comprises the claimed KRRLIFSK sequence," (Paper No. 16, page 3). This reference discloses the full-

length nucleotide and amino acid sequence of p21. Xiong *et al.* do not teach particular regions or fragments of p21, or suggest that anything less than the intact, full-length p21 protein might be useful. In contrast, the present methods use a *peptide fragment of p21*, (*i.e.*, less than full-length p21). In the absence of such teachings, one skilled in the art presented with the teachings of Beach *et al.* and Xiong *et al.*, could not have predicted that fragments of p21 containing the claimed KRRLIFSK sequence would be useful in the presently claimed methods.

In view of the above, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified Application, the Examiner is invited to call the undersigned at (617) 227-7400.

Date: July 23, 2002

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APPENDIX I- Pending Claims

2. A method for identifying a compound which modulates interaction or binding between p21 and cyclin D1, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1, or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

3. The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 4 (SEQ ID NO:4).

4. The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence **K**xxRRyFz**P** (SEQ ID NO:14).

5. The method according to claim 4 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 2 (SEQ ID NO:2).

6. The method according to claim 2, 44 or 45 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence xyLzF.

7. The method according to claim 6 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 10 (SEQ ID NO:10).

8. The method according to claim 6 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence KRRLIFSK (SEQ ID NO:23).

9. The method according to claim 8 wherein the fragment, derivative or analog of p21 comprises the amino acid sequence of peptide 11 (SEQ ID NO:11).

10. The method according to claim 2, 44 or 45 further comprising testing the ability of the compound to modulate a p21- mediated effect on Cdk4 activity.

11. A method according to claim 10 wherein RB phosphorylation is tested.

12. A method according to claim 2, 44 or 45 wherein induction of G1 cell-cycle arrest is tested.

17. A method comprising obtaining a compound which modulates the interaction or binding between p21 and cyclin D1 in accordance with claim 2, further comprising formulating the compound into a composition including at least one additional component.

44. A method for identifying a compound which modulates interaction or binding between p21 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising Cdk4 or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

45. A method for identifying a compound which modulates interaction or binding between p21, cyclin D1 and Cdk4, the method including:

(a) bringing into contact a first substance which includes a peptide fragment of p21, or a derivative or analog thereof, comprising an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4) (SEQ ID NO:4);

KACRRLFGPVDSEQLSRDCD (peptide 2) (SEQ ID NO:2);

KxxRRyFz**P** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the bold residues may be absent or different); (SEQ ID NO:14)

KRRQTSMTDFYHSKRRLIFS (peptide 10) (SEQ ID NO:10);

KRRQTSATDFYHSKRRLIFS (SEQ ID NO:28);

TSMTDFYHSKRRLIFSKRKP (peptide 11) (SEQ ID NO:11);

KRRLIFSK (SEQ ID NO:23); and

xyLzF (wherein y and z are any amino acid and x is preferably R),

with a second substance comprising cyclin D1 and Cdk4, or a derivative or analog thereof, and a test compound, under conditions wherein, in the absence of the test compound being an inhibitor of interaction or binding of said first and second substances, said first substance and said second substance interact or bind; and

(b) determining interaction or binding between said first substance and said second substance.

46. A method comprising obtaining a compound which modulates the interaction or binding between p21 and Cdk4 in accordance with claim 44, further comprising formulating the compound into a composition including at least one additional component.

47. A method comprising obtaining a compound which modulates the interaction or binding between p21, cyclin D1 and Cdk4 in accordance with claim 45, further comprising formulating the compound into a composition including at least one additional component.

51. The method of claim 2, 44 or 45 wherein the peptide fragment of p21 is about 40 amino acids or less.

52. . The method of claim 2, 44 or 45 wherein the peptide fragment of p21 is about 35 amino acids or less.

53. The method of claim 2, 44 or 45 wherein the peptide fragment of p21 is about 30 amino acids or less.

54. The method of claim 2, 44 or 45 wherein the peptide fragment of p21 is about 25 amino acids or less.

55. The method of claim 2, 44 or 45 wherein the peptide fragment of p21 is about 20 amino acids or less.

56. The method of claim 2, 44 or 45 wherein the peptide fragment of p21 is about 10 amino acids or less.